Long-term exposure to PM2.5 and fasting plasma glucose in non-diabetic adolescents in Yogyakarta, Indonesia

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Abstract

Background: Indonesia is facing serious air pollution. However, very few studies have been conducted to examine the health risks of air pollution in Indonesia, particularly for adolescents.

Objective: To assess the association between long-term exposure to ambient particles with a diameter of < 2.5 μm ($PM_{2.5}$) and fasting plasma glucose (FPG) in adolescents.

Methods: A cross-sectional study was conducted in 482 adolescents aged 14-18 years in Yogyakarta, Indonesia in 2016. We finally included 469 (97.30%) participants who had no missing data for data analysis. We collected individual data on socio-demographics, behavioral habits, and health information through standardized questionnaires. Satellite-based $PM_{2.5}$ concentrations from 2013 to 2016 were assigned based on participants' residential address. The association between $PM_{2.5}$ and FPG was examined using a generalized linear regression model while FPG was modeled as a continuous variable. An ordered logistic regression model was used to assess the relationship between $PM_{2.5}$ and FPG categories.

Results: Every 1 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 0.34 mg/dL [95 confidence interval (95% CI): 0.08 mg/dL, 0.59 mg/dL] increase in FPG levels. Comparing with the low FPG level (under 86 mg/dL), every 1 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 10.20% (95% CI: 1.60%, 19.80%) increase in the odds of impaired fasting glucose (IFG) (100 to 125 mg/dL). Stratified analyses indicated greater effects on participants with hypertension [odds ratio (OR) = 1.30, 95% CI: 1.09, 1.57]

and those had higher physical activities (OR = 1.36, 95% CI: 1.09, 1.57). Adolescents' sex, obesity status and different cutoff points of FPG did not modify the association between the exposure to $PM_{2.5}$ and FPG levels.

Conclusion: Long-term exposure to $PM_{2.5}$ was associated with increased FPG levels in Indonesian non-diabetic adolescents.

Keywords: $PM_{2.5}$; long-term; fasting plasma glucose; diabetes; Indonesia

Capsule： Long-term exposure to $PM_{2.5}$ was associated with higher FPG levels in adolescents without diabetes in Indonesia, which provides scientific evidence for elevated fasting plasma glucose risk related to $PM_{2.5}$ exposure.

1. Introduction

Diabetes is a group of metabolic disorders featured by insulin resistance (IR), a progressive loss of β-cell, and high blood glucose levels (American Diabetes Association, 2019), and has been considered being one of the top causes for disability (Alam et al., 2019). At present, approximately half a billion people live with diabetes across the globe, and this figure is expected to increase to 693 million by 2045 (Cho et al., 2018). Developing countries carry the major burden of diabetes (Ogurtsova et al., 2017). Indonesia is one of the top ten countries for the number of people with diabetes with 10.3 million in 2017 (International diabetes federation, 2017) and the trend is still rising.

Diabetes can be diagnosed based on fasting plasma glucose (FPG) value (American Diabetes Association, 2019), while high FPG has become the third-leading risk factor for deaths, accounting for more than 5.6 million deaths globally (Alam et al., 2019; Gakidou et al., 2017). Both World Health Organization (WHO) and the American Diabetes Association (ADA) (Shaw et al., 2006) regard high FPG as one of the high-risk factors for diabetes and it can be employed independently to predict diabetes risk (Tirosh et al., 2005). Therefore, the early prevention of high FPG is crucial.

Particulate matter with a diameter of less than 2.5 micrometers ($PM_{2.5}$) is one of the

most global concerns (Gakidou et al., 2017). In Indonesia, air pollution has been considered as a national problem with a serious impact on human health (Haryanto, 2018; Hayasaka et al., 2014; Santoso et al., 2013). A study indicated that air pollution has caused 50% of morbidity across Indonesia (Haryanto and Franklin, 2011), while the total proportion of $PM_{2.5}$ increase is predicted up to 26% by 2030 in the country (Haryanto, 2018).

Epidemiological investigations have indicated that exposure to $PM_{2.5}$ is associated with adverse health outcomes (Atkinson et al., 2014) and is responsible for cardiovascular and respiratory morbidity and mortality (Atkinson et al., 2014; Hoek et al., 2013). Recent research has reported that $PM_{2.5}$ is associated with diabetes (Eze et al., 2015; Lee et al., 2019; Yang et al., 2018). Meanwhile, growing studies (Chen et al., 2016; Chuang et al., 2011; Liu et al., 2016; Peng et al., 2016; Yang et al., 2018) indicated that ambient $PM_{2.5}$ contribute to high FPG in adults. However, few research (Toledo-Corral et al., 2018) focused on the association between $PM_{2.5}$ and FPG levels in children, especially in adolescents.

Compared to adults, adolescents have higher respiratory and metabolic rates, rapidly dividing cells, and immature immune system (Worthman et al., 2019). As a result, they are more susceptible to agents absorbed through the pulmonary route than adults. Moreover, the increasing prevalence of adolescent obesity (Abarca-Gómez et al., 2017)

is also exacerbating the adverse health effects of $PM_{2.5}$, because obese adolescents inhale the greater volume of air than their peers with normal weight (Kawasaki et al., 2012). Considering the above mentioned differences between adults and adolescents, as well as the accentuated adverse effects of $PM_{2.5}$ in people with obesity compared to those with healthy weight status, it is important to explore the relationship between $PM_{2.5}$ and FPG in both overweight/obese adolescents and those of healthy weight.

In addition, most relevant studies were conducted in developed countries (Chen et al., 2016; Eze et al., 2015; Peng et al., 2016; Toledo-Corral et al., 2018), while few studies were reported in developing countries like China (Cai et al., 2019; Yang et al., 2018; Liu et al., 2016) and India (Curto et al., 2019), where the prevalence of diabetes and air pollution levels are significantly different from Southeast Asia (Rumney, 2010). The association between the exposure to $PM_{2.5}$ and FPG in Indonesian populations has not been well investigated. Therefore, in this study, we aimed to assess whether long-term exposure to $PM_{2.5}$ is associated with FPG in non-diabetic adolescents in Indonesia.

2. Methods

2.1 Study participants

A cross-sectional study was conducted between January 1 and December 31, 2016 in Yogyakarta, a city in the southern part of Java Island, Indonesia. The adolescents were

recruited from ten public and private senior schools. At each school they were randomly selected using a random numbers generator from the students' identity list. The entry criterion included the subject who was a long-term resident at the place, while the patients with diabetes (FPG of 126 mg/dL or above) or other cardiovascular diseases were excluded in this study. The initial study was aimed to investigate the role of vitamin D deficiency in cardiovascular disease risk factors development in obese adolescents. For that reason, 4268 students were screened for obesity using the three body mass index (BMI) reference cut-points: WHO criterion (Onis et al., 2007), the International Obesity Task Force (IOTF) grade (Cole et al., 2000), and the US Centers for Disease Control (CDC) percentile (Kuczmarski et al., 2002). In order to be considered overweight or obese, participants must be obese or overweight under all criteria of the WHO, IOTF, and US CDC. The screening was done between January to February 2016. An ethics approval was obtained from the Ethics Committee at Universitas Gadjah Mada, Yogyakarta, Indonesia for the initial study (No. KE/FK/333/EC/2016). For the present study, a minimum of 200 overweight/obese and 200 normal-weight participants were required to achieve sufficient statistical power. To be specific, a stratified random sampling method was used with an approximately 1:10 sampling ratio in both overweight/obese and normal weight groups. A total of 482 adolescents between 14 and 18 years of age agreed to participate in the study (Table S1) and informed consents were obtained from their parent/guardian. Another ethics approval from the same Ethics Committee was obtained (KE/FK/0104/EC/2019). The study adhered to ethical principles for Medical Research according to Declaration of

141 Helsinski.

142

143 We collected socio-demographics, health-related behaviors, and other health-related
144 information via a standardized questionnaire. Individual basic information consisted of
145 age, sex, home address, secondhand smokers (no, yes), and smoking status (no, yes).
146 The International Physical Activity Questionnaire-Short Form (IPAQ-SF) was used to
147 assess physical activity behavior in participants with overweight or obesity (Lee et al.,
148 2011). All participants were measured three times with their barefoot standing height
149 with a measuring tape attached to the wall and weight with minimal clothing. Both
150 measurements to their means were recorded with the nearest 0.1 cm or 0.1 kg. The body
151 mass index was calculated as the body weight (kg) divided by the squared body height
152 (m^2). Blood pressure was measured by using an automatic blood pressure monitor in a
153 quiet state. Finally, we included 469 (97.50%) participants who had no missing values
154 for data analysis (Figure S1), of which 233 (49.70%) participants were overweight or
155 obese.

156

157 2.2 Fasting plasma glucose measurement and categories

158 After overnight fasting, blood samples and FPG levels were collected for each
159 participant between March and April in 2016. FPG was measured using the hexokinase
160 method. According to the ADA criteria, FPG less than 100 mg/dL corresponds to

normal levels, the 100-125 mg/dL range to impaired fasting blood glucose (IFG), and FPG greater than 126 mg/dL is defined as clinical diabetes (American Diabetes Association, 2017). However, the current criteria are not age specific and FPG is known to increase with age(Chia et al., 2018). We used the moderate value (86 mg/dL) of FPG as a cut-off point to split the normal FPG levels of adolescent, which aligned with a 21-year cohort research (Nguyen et al., 2010). Our sensitivity analysis of different cut-off points also showed that this cut-point had the highest adjusted odds ratio (OR) in the interquartile range (IQR) of FPG. Finally, we divided FPG into three categories (moderate levels with FPG less than 86 mg/dL, moderate-high levels with FPG 86-99 mg/dL, and IFG group with FPG 100-125 mg/dL).

2.3 Ambient air pollution assessment

We are authorized to obtain the annual mean $PM_{2.5}$ data from Atmospheric Composition Analysis Group. They estimated the global annual ground-based $PM_{2.5}$ concentrations at 0.01°×0.01° (approximately 1.1 km × 1.1 km) spatial resolution using a Geographically Weight Regression by combining satellite, models, and monitors methods (Van Donkelaar et al., 2016). We used four-year (2013-2016) average of $PM_{2.5}$ concentrations as a surrogate of participants' long-term exposure to ambient $PM_{2.5}$. The $PM_{2.5}$ data were assigned to individuals according to their residential address.

2.4 Statistical analysis

Data are presented as mean [standard deviation (SD)] for continuous normally distributed variables, median [IQR] for continuous non-normal distributed variables, or number (percentage) for categorical variables. All continuous variables were tested for normality using a Shapiro Wilk test. We tested the contrasts in baseline characteristics in the FPG groups using Kruskal-Wallis Rank Sum Test for non-normal variables and χ^2 test for categorical variables with a priori α level of 0.05 to determine statistical significance. Our initial analysis showed that FPG was following normal distribution.

Due to the features of data, in the analysis, the linearity assumptions of the covariates were checked by using cubic splines and there was no deviation from linear dose response (Figure S2). We therefore applied a generalized linear regression model to assess the association between $PM_{2.5}$ exposure and continuous FPG, whereas ordered logistic regression models to assess the relationship between ambient air pollution and FPG categories (under 86 mg/dL, 86 to 99 mg/dL, and 100 to 125 mg/dL).

We firstly treated FPG as a continuous variable and a generalized linear regression model was established, as our preliminary analyses showed a linear relationship between $PM_{2.5}$ and FPG. Best fit of the model was produced using the step backward regression with the lowest value of Akaike Information Criterion (AIC). The final

adjusted model included age, sex, smoking status (no, yes), diastole blood pressure, and obesity status (normal, overweight or obese).

In the secondary analysis, we categorized FPG by using 86 mg/dL and 100 mg/dL as cutoff points to apply ordered logistic regression models. The proportional odds assumption or the parallel regression assumption was evaluated which assumed that the relationship between each pair of outcome groups was the same. Therefore, there was only one set of ORs. In the ordered logistic regression model, $PM_{2.5}$ was considered as the key exposure variable and confounders included age, sex, smoking status, diastole blood pressure, and weight status. Results were expected as beta coefficients for continuous FPG and as OR for FPG categories (the under 86 mg/dL category was the comparison group).

We performed subgroup analyses by sex, weight status, smoking status, secondhand smoking, and blood pressure categories to examine which group is more affected by $PM_{2.5}$. All statistical analysis was performed using R software (version 3.5.3). The "MGCV" and "VGAM" packages were used to fit the generalized linear regression and ordered logistic regression models, respectively.

2.5 Sensitivity analyses

221 Sensitivity analyses were performed to evaluate the robustness of the results (Table S2).
222 In order to check the different impacts of each year's $PM_{2.5}$ concentration, we put each
223 year's $PM_{2.5}$ from 2013 to 2016 into the models separately. Three different obesity
224 criteria were compared to assess the robustness of our classification for weight status.
225 Moreover, we did additional sensitivity analyses using different cutoff points to divide
226 the normal FPG range (< 100 mg/dL) into two groups (moderate level group and
227 moderate-high level group) to evaluate the robustness of our findings.

228

229 3. Results

230 There were a total of 469 adolescents included for data analysis (Figure S3), with an
231 average age of 16.30 years (SD = 0.66 years) ranging from 14.96 to 17.95 years, and
232 270 (57.40%) were males. Table 1 shows the characteristics of adolescents stratified by
233 three FPG categories (moderate levels, moderate-high levels, and the IFG group). There
234 were 259 (55.10%) participants with the moderate FPG level and 197 (41.90%)
235 participants in the moderate-high level group. The prevalence rate of IFG was 3% (13
236 participants) in our study. In the study, males were more likely to have a higher FPG
237 (86.04±7.06 mg/dL) than females (84.52±7.04 mg/dL).

238

239 Table 1 Characteristics of the study participants by fasting plasma glucose categories

FPG categories	Participants with moderate FPG levels (N = 259)	Participants with moderate-high FPG levels (N = 197)	Participants with IFG (N = 13)	Total (N = 469)	p value
Age (years)	16.33 (0.67)	16.23 (0.64)	16.21 (0.70)	16.29 (0.66)	0.21
Sex (%)					
Male	135 (52.10)	125 (63.50)	10 (76.90)	270 (57.40)	
Female	124 (47.90)	72 (36.50)	3(23.10)	199 (42.60)	0.02
BMI, z-score	0.78 [-0.57, 2.41]	2.16 [-0.31, 2.57]	2.21 [-0.09, 2.74]	0.98 [-0.45, 2.52]	0.11*
Weight status (%)					
Normal	142 (54.80)	89 (45.20)	5 (38.50)	236 (50.30)	
Overweight/obese	117 (45.20)	108 (54.80)	8 (61.50)	233 (49.70)	0.09
Smoking (%)					
Yes	14 (5.40)	18 (9.10)	0 (0.00)	32 (6.80)	
No	245 (94.60)	179 (90.90)	13 (100.00)	437 (93.20)	0.17

Physical activity in overweight/obese participants (%)					
Moderate or high	40 (46.50)	41 (48.80)	2 (40.00)	83 (47.40)	
Low	46 (53.50)	43 (51.20)	3 (60.00)	92 (52.60)	0.54

Data are presented as mean (standard deviation), median [interquartile range], or number (percentage).

Moderate FPG levels: FPG less than 86 mg/dL; Moderate-high FPG levels: FPG 86-99 mg/dL; IFG levels: FPG 100-125 mg/dL.

FPG: fasting plasma glucose; IFG: impaired fasting glucose; BMI: body mass index.

*: nonparametric tests.

Table 2 presents the annual average ambient $PM_{2.5}$ concentrations from 2013 to 2016 in the residence of sampling adolescents. The concentrations varied slightly across different years, with range from 10.75 to 25.50 μg/m³ . $PM_{2.5}$ level in those four years exceeded the WHO standard for annual concentration (10 μg/m³) (Krzyzanowski and Cohen, 2008).

Table 2 Distribution of $PM_{2.5}$ concentrations from 2013 to 2016

Annual $PM_{2.5}$ (N = 469)	Median [IQR]	Mean (SD)	% of > WHO standard
2013	19.00 [15.00, 19.00]	17.29 (2.52)	99.40
2014	21.00 [17.00, 21.00]	19.30 (2.50)	100.00
2015	20.00 [16.00, 20.00]	18.57 (2.40)	99.40
2016	24.00 [20.00, 24.00]	22.50 (2.36)	100.00
4 years average	21.00 [17.30, 21.00]	19.42 (2.42)	100.00
p value	< 0.01	< 0.01	

$PM_{2.5}$: particulate matter with a diameter of < 2.5 μm; IQR: interquartile range; SD: standard deviation.

WHO standard for annual $PM_{2.5}$: 10 μg/m³ (Krzyzanowski and Cohen, 2008)

Results of generalized linear regression model and ordered logistic regression are presented in Table 3. There was a positive association between $PM_{2.5}$ levels and FPG, whereby, exposure to a 1 μg/m³ increase in the annual level of $PM_{2.5}$ was associated with a 0.34 mg/dL [95% confidence interval (95% CI): 0.08 mg/dL, 0.59 mg/dL] increase in FPG while controlling for age, sex, smoking, blood pressure, and weight status. Results of the ordered logistic regression indicated that 1 μg/m³ increase in $PM_{2.5}$ exposure level for adolescents was associated with a 10.20% increase in the odds of having higher FPG. Adjusted OR of participants with IFG/ FPG at moderate-high levels

versus moderate levels associated to an increase in $PM_{2.5}$ pollutant level was 1.10 (95% CI: 1.02,1.20).

266 Table 3 Association between $PM_{2.5}$ exposure and fasting plasma glucose in non-diabetic adolescents in Yogyakarta, Indonesia

	Generalized Linear Regression Outcome: continuous FPG			Ordered Logistic Regression Outcome: FPG categories		
	Adjusted β (95% confidence interval)	p value	p-value for interaction	Adjusted OR (95% confidence interval)	p value	p-value for interaction
Total (N = 469)	0.34 (0.08,0.59)	0.01		1.10 (1.02,1.20)	0.02	
Sex			0.69			0.71
Male (N = 270)	0.33 (-0.05,0.72)	0.09		1.11 (0.99,1.24)	0.08	
Female (N = 199)	0.32 (-0.02,0.65)	0.06		1.10 (0.97,1.24)	0.14	
Weight status			0.55			0.97
Normal (N = 236)	0.39 (0.07,0.70)	0.02		1.11 (0.99,1.24)	0.07	
Overweight/obese (N = 233)	0.27 (-0.16,0.70)	0.22		1.10 (0.97,1.25)	0.15	
Blood pressure categories						
Normal (N = 318)	0.30 (0.02,0.59)	0.04		1.07 (0.97,1.18)	0.19	
Prehypertension (N = 48)	-0.62 (-1.78,0.54)	0.30	0.03	0.87 (0.97,1.18)	0.31	0.19
Hypertension (N = 95)	0.72 (0.17,1.28)	0.01	0.30	1.30 (1.09,1.57)	0.01	0.79
Physical activity			0.68			0.78

Moderate/High (N = 83)	1.09 (0.40,1.77)	< 0.01	1.36 (1.09 1.57)	0.01
Low (N = 92)	-0.12 (-0.70,0.47)	0.70	0.96 (0.95 1.20)	0.69

Both models adjusted for age, sex, smoking status, diastolic blood pressure levels, weight status.

Adjusted OR of participants with IFG/ FPG at moderate-high levels versus moderate levels associated to an increase in $PM_{2.5}$ pollutant level.

Interaction: sex, overweight/ obesity, blood pressure categories, or physical activity interact with $PM_{2.5}$.

Blood pressure categories: normal - SBP (systolic blood pressure) < 120 mmHg and DBP (diastolic blood pressure) < 80 mmHg; prehypertension - SBP 120-129 mmHg and DBP < 80 mmHg; hypertension - SBP > 130 mmHg or DBP > 80 mmHg.

$PM_{2.5}$: particulate matter with a diameter of < 2.5 μm; FPG: fasting plasma glucose; OR: odds ratio.

We also conducted stratified analyses by sex, weight status, blood pressure levels, and physical activity (Table 3). The increase in FPG risk appeared to be larger for individuals with hypertension (OR = 1.30, 95% CI: 1.09, 1.57) and those had higher physical activities (OR = 1.36, 95% CI: 1.09, 1.57).

Sensitivity analyses showed that the association between $PM_{2.5}$ and FPG was similar when using different obesity criteria (Table S3) and different years' exposure (2013-2016) (Table S4). Moreover, we assessed the effects of changing the cutoff points of glucose levels and found that the associations of $PM_{2.5}$ concentrations with FPG did not change (Figure 1, Table S5). The results indicated that the cut-point of 86 mg/dL had the highest adjusted OR in the IQR of FPG (81-89 mg/dL).

4. Discussion

To the best of our knowledge, this is the first study to examine the association between $PM_{2.5}$ exposure and FPG in adolescents in Indonesia. We observed that a 1 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with 0.34 mg/dL increase in FPG. We also observed that compared with participants with moderate FPG, an increase in $PM_{2.5}$ level (1 $\mu g/m^3$) was associated with a 10.20% increase in the odds of having moderate-high FPG or IFG risk.

Our results of this study are consistent with a previous epidemiological research in Los Angeles (United States) (Toledo-Corral et al., 2018), which showed that $PM_{2.5}$ was associated with an increased risk of high FPG. That study explored the relationship

between air pollution exposure and glucose metabolism in 429 overweight and obese minority children in Los Angeles (United States) and reported that the cumulative 12-month $PM_{2.5}$ were associated with a 1.7% higher fasting glucose. It is important to mention that although this study, along with ours, showed a positive association between $PM_{2.5}$ exposure and FPG, the reported association (1.55 mg/dL increase per 1 $\mu g/m^3$ increase in $PM_{2.5}$) was slightly higher than our result (0.34 mg/dL increase per 1 $\mu g/m^3$ increase in $PM_{2.5}$). The main difference is that the previous study mainly focused on overweight and obese minority children, whereas our study concentrated on both normal weight youth and obese or overweight ones. Moreover, it should be with cautions to compare the results of our study with this previous investigation directly because it consisted of obese children with a higher basic fasting glucose levels (89.00±6.80 mg/dL), while in our study, participants came from adolescents aged 14-18 years who were likely to have a lower basic fasting glucose (85.50±7.08 mg/dL). Several other previous studies in adults (Chen et al., 2016; Chuang et al., 2011; Dong et al., 2015; Liu et al., 2016; Peng et al., 2016; Yang et al., 2018) have explored the similar association between $PM_{2.5}$ exposure and FPG which were consistent with ours.

Prediabetes has been proved to be the risk state to the increased incidence of diabetes and cardiovascular disease (Unwin et al., 2002; Williams et al., 2005). Even though ADA identified people with prediabetes IFG and also adjusted the diagnostic cutoff point for IFG from 110 mg/dL to 100 mg/dL in early 2004, this criterion is not age-specific (American Diabetes Association, 2017; Shaw et al., 2006). A cohort of 12119 school-aged children in Taiwan showed an optimal threshold of 85.50 mg/dL for participants aged 6-11 years and 93.50 mg/dL for those aged 12-18 years (Yang et al.,

2019). Another retrospective cohort study found a more than 2-fold increased risk of developing adult prediabetes and type 2 diabetes in children with 86 to 99 mg/dL fasting blood glucose (FBG) compared with less than 86 mg/dL group (Nguyen et al., 2010). Other studies were also in agreement with the point that higher FPG levels within the normoglycemic range contribute to the increase of type 2 diabetes (Tirosh et al., 2005). In our study, we used a cutoff point (86 mg/dL) to categorize the normoglycemic range of FPG levels. We observed that compared with participants with less than 86 mg/dL FPG, $PM_{2.5}$ level was associated with a 10.20% increase in the odds of having higher FPG. In the meantime, we changed different cutoff points of glucose levels, but it did not modify the associations.

The underlying biological mechanisms for the association between $PM_{2.5}$ and FPG have not been entirely clear. A study in animals has shown that pregnant mice exposed to $PM_{2.5}$ during the whole gestation could lead to cardiac hypertrophy and the increase in FPG levels (Wu et al., 2019). One plausible explanation is that long-term exposure to $PM_{2.5}$ alters the balance in adipose tissue, induces oxidative stress and visceral inflammation (Sun et al., 2005), leading to endoplasmic reticulum stress, apoptosis and insulin signaling abnormalities, which further results in metabolic disturbances (Sun et al., 2009). Systemic inflammation is another potential mechanism for the association between air pollution and FPG (Morteza, 2013). Air pollution causes cell injury in lung and generates a rich milieu of inflammatory mediators (Mills et al., 2009). They could be indirectly released into the blood or systemic circulation with direct action at the target sites, which might lead to systemic inflammatory reaction and mediate adverse effects on the cardiovascular system and modify the average plasma glucose level

(Brook et al., 2010). Other possible pathways include the changes of unfolded protein (UPR)/endoplasmic reticulum (ER) stress in adipose tissue (Mendez et al., 2013), the alterations in brown adipose tissue (BAT) and mitochondrial dysfunction (Rajagopalan and Brook, 2012), and the decline in insulin signaling in the liver, causing the impairment of hepatic IR (Rao et al., 2014). On the basis of these findings, our results provide possible supports for $PM_{2.5}$ exposure related to elevated FPG risk.

As we have mentioned above, adolescents in our study were classified as overweight or obese based on three sets of BMI cut-points: IOTF, WHO, and CDC. Considering the difference in age-specific BMI cut-offs (Shields and Tremblay, 2010), our participants were judged to be obese or overweight with a more stringent standard (meeting all three criteria simultaneously). An increasing number of researches have reported a positive association between air pollution and childhood obesity (de Bont et al., 2019; Dong et al., 2015). In our stratified analysis by weight status, we adjusted the impact of overweight/obesity, but there was no significant difference in the $PM_{2.5}$-FPG association between overweight/obese and normal weight groups. This implies that elevated $PM_{2.5}$ concentrations appear to have independent adverse effects on FPG.

Physical activity has been wildly considered as a confounder in exploration of the association between air pollution and glucose metabolism (Chuang et al., 2011; Liu et al., 2016), because people with high physical activity, especially outdoor physical activity, might have higher actual air pollution exposure (Roberts et al., 2014; Yu et al.,2017). In our study, we quantified the physical activity in overweight/obese participants using an IPAQ-SF questionnaire and found that the risk in FPG tended to

be larger for participants who had higher physical activity than those with low intensity. However, it should be cautious to explain the impacts of physical activity on the association between $PM_{2.5}$ and FPG due to the lack of investigation for the normal weight participants in our study. Hence, further studies are warranted to explore the joint impacts physical activity and air pollution on glucose metabolism.

In other stratified analyses, the associations between $PM_{2.5}$ and FPG were significantly different for individuals with hypertension than those with normal blood pressure. One possible explanation is that since FPG and air pollution are both related to increased inflammation, people with hypertension would be more likely to be susceptible to the inflammatory effects, further resulting in the prevalence of hypertension (Dong et al., 2015; Pauletto and Rattazzi, 2006).

Our study has several strengths. Our sample consists of non-diabetic adolescents in Indonesia, a developing country with a special geographic location and climatic diversity, where the number of people with diabetes ranked one of the top ten in the world (International diabetes federation, 2017). Few studies have explored the association between ambient air pollutants and FPG in adolescents (Toledo-Corral et al., 2018). We explored the long-term exposure to $PM_{2.5}$ at the residential address for four years, and standardized questionnaires were used to assess the health-related information and physical activity levels. We estimated the association of long-term exposure to $PM_{2.5}$ with FPG in non-diabetic adolescents and regarded FPG as a continuous variable and classified it using suitable cutoffs to explore the risk at high glucose metabolism in adolescents.

Our study still has several limitations. Considering the cross-sectional design of this study, it is difficult to establish causality between $PM_{2.5}$ exposure and FPG. Though we used the exposure of $PM_{2.5}$ from 2013 to 2016 and measured glucose-related markers in 2016, as the markers were measured at a single time point, it was difficult to disentangle the causal association between $PM_{2.5}$ and FPG. Though we adjusted for several potential confounders (sex, physical activity, weight status, smoking, blood pressure levels) and conducted plenty of sensitivity analyses, the possibility of socioeconomic confounding effect (including family economic status, parental education, and medical conditions) cannot be ruled out completely. We were unable to take into consideration of time activity patterns in adolescents. Although we assessed the impacts of physical activity for overweight/obese participants on the association of $PM_{2.5}$ with FPG, it is notable that adolescents tend to have a substantial change in physiological aspects and habits during adolescent stage because of puberty (Adams and Berzonsky, 2008). The concentrations of $PM_{2.5}$ were just based on residential exposure, which may lead to exposure misclassification and attenuate the observed effects (Nerriere et al., 2005). The ambient air pollution inhales dose on personal levels is warranted to be collected. Since parts of the information in our study was based on the collection of questionnaires and not all participants provided blood samples, information and selection biases were possible. Detailed short-term exposure to $PM_{2.5}$ and the long-term cumulative effect were not available in our study. We used 4-year average exposure as long-term exposure to reflect the background $PM_{2.5}$ levels. However, short-term and traffic-related air pollution exposure is needed to obtain more insight into the association in future studies. Last, our results may not be generalizable

to populations with other different age-stages from high-income countries where $PM_{2.5}$ concentrations are obviously different.

In summary, this study indicates that long-term exposure to $PM_{2.5}$ was associated with higher FPG levels in adolescents without diabetes in Indonesia, implying that higher FPG levels even in the normoglycemic range (less than 100 mg/dL) were related to $PM_{2.5}$ exposures. Our results are of significance to public health. FPG is one of the most commonly used indicators for diabetes (Brambilla et al., 2011), reflecting β-cells function, generally indicating the secretion function of basic insulin. While constant elevation in high glucose would result in glucose toxicity, which exerts adverse pathological effects on multiple organ systems, such as decreased insulin secretion in the endocrine system and endothelial cell dysfunction in the vascular system (Wasserman, 2009). The results of our study indicate that long-term exposure to $PM_{2.5}$ is associated with higher plasma glucose, which may consequently increase the risk of developing diabetes among adolescents. This conclusion provides scientific evidence for elevated FPG risk related to $PM_{2.5}$ exposure. It also encourages policymakers to focus on the improvement of air quality to reduce the risks of diabetes. However, due to the limitations in our study, the results should be interpreted with caution, and future cohort-based studies in large populations are needed to determine the causal relationship.

Declaration of interests

We declare no competing interests.

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Figure legend:

Figure 1 Odds ratios of different cutoff points of fasting plasma glucose

*: Odds ratios are statistically significant with $p < 0.05$.